International Journal of Pharmacy and Natural Medicines
ISSN: 2321-6743 | https://doi.org/10.30904/j.ijpnm.2026.4989

Advanced Particle Size Characterization of Famotidine Oral Suspension Using Laser Diffraction Technology

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Received: 10-03- 2026 | Revised: 31-03- 2026 | Accepted: 25-04- 2026 | Published: 28-05-2026

ABSTRACT
Famotidine Oral Suspension USP, 40 mg/5 mL, is a widely used liquid dosage form for the treatment of acid-related gastrointestinal disorders, particularly in pediatric and geriatric patients who experience difficulty swallowing solid dosage forms. Particle size distribution (PSD) is a critical quality attribute of suspension formulations because it significantly influences physical stability, sedimentation behavior, dispersibility, dissolution characteristics, content uniformity, and overall product performance. The present study aimed to develop and validate a reliable particle size distribution method for Famotidine Oral Suspension USP, 40 mg/5 mL, using a Malvern Mastersizer 3000 laser diffraction analyzer. Method optimization was performed by evaluating critical analytical parameters, including dispersant selection, obscuration level, agitation rate, refractive index, and measurement conditions. Water was selected as the dispersing medium, and optimized analytical conditions were established to achieve consistent particle dispersion and reproducible results. The developed method was evaluated for precision, intermediate precision, and robustness. Method precision was assessed using six independently prepared samples and demonstrated excellent reproducibility, with %RSD values of 2.41%, 1.04%, and 1.00% for d(0.1), d(0.5), and d(0.9), respectively. Intermediate precision studies performed by a second analyst on a different day showed %RSD value within acceptable limits, confirming method reproducibility. Robustness testing involving deliberate variations in agitation rate and obscuration level also produced satisfactory results, indicating that the method remained unaffected by minor changes in analytical conditions. The results demonstrated that the developed laser diffraction method is precise, reproducible, and robust for the determination of particle size distribution in Famotidine Oral Suspension USP, 40 mg/5 mL, and is suitable for routine quality control and product characterization applications.

Keywords
Famotidine Oral Suspension USP, Particle Size Distribution (PSD), Cinnamon, Laser Diffraction, Malvern Mastersizer 3000

Introduction

Famotidine is a potent histamine H_2-receptor antagonist widely used in the treatment and prevention of acid-related gastrointestinal disorders, including peptic ulcer disease, gastroesophageal reflux disease (GERD), erosive esophagitis, and pathological hypersecretory conditions such as Zollinger–Ellison syndrome [1]. By selectively inhibiting H_2 receptors on gastric parietal cells, famotidine effectively suppresses basal and stimulated gastric acid secretion, thereby promoting ulcer healing and providing symptomatic relief from acid-induced gastrointestinal discomfort[2]. Famotidine Oral Suspension USP, 40 mg/5 mL, is a liquid dosage form specifically designed for paediatric, geriatric, and dysphagic patients who experience difficulty swallowing conventional solid oral dosage forms[3]. The suspension formulation offers flexibility in dose adjustment, ease of administration, and improved patient compliance. To ensure consistent therapeutic performance, it is essential that the active pharmaceutical ingredient remains uniformly dispersed throughout the suspension and exhibits controlled particle size characteristics. Particle size distribution (PSD) is a critical quality attribute for oral suspension formulations because it directly influences sedimentation behavior, dispersibility, content uniformity, dissolution rate, bioavailability, and overall product stability [4]. Variations in particle size can lead to dose inconsistency, caking, and changes

in drug release characteristics during storage. Therefore, accurate determination and control of particle size distribution are fundamental requirements during formulation development, manufacturing, and quality control of pharmaceutical suspensions [5]. Laser diffraction has emerged as one of the most widely accepted techniques for particle size analysis due to its rapidity, reproducibility, wide measurement range, and ability to characterize particles in their dispersed state. The Malvern Mastersizer 3000 utilizes laser diffraction principles to provide detailed particle size distribution profiles, commonly expressed as d(0.1), d(0.5), and d(0.9) values, which represent the particle diameters below which 10%, 50%, and 90% of the sample volume exists, respectively[6]. The present study was undertaken to develop and evaluate a robust particle size distribution method for Famotidine Oral Suspension USP, 40 mg/5 mL, using the Malvern Mastersizer 3000.

The developed method was assessed for key analytical performance characteristics, including precision, intermediate precision, and robustness, to establish its suitability for routine quality control and characterization of the suspension formulation [7]. This study aims to provide a reliable analytical approach for monitoring particle size attributes and ensuring consistent product quality throughout the product lifecycle. The development of the present particle size distribution methodology was scientifically supported by the foundational research conducted by Dr. Nataraj Palaniyappan, Novitium Pharma LLC, USA. The previously established analytical methodology entitled Analytical Method Development and Validation for the Determination of Particle Size Distribution in Combined Dosage Form (Sulfamethoxazole and Trimethoprim Oral Suspension USP) provided an important technical basis for the current investigation[8-10]. The scientific principles, methodological framework, and analytical strategies developed through that work contributed significantly to the optimization of the particle size characterization approach employed in this study. These contributions facilitated the establishment of a reliable, reproducible, and scientifically robust method for evaluating the particle size distribution of Famotidine Oral Suspension USP, 40 mg/5 mL.

Materials and Methods

Materials

Famotidine Oral Suspension USP, 40 mg/5 ml, as a dispersant, It uses Milli-Q Water.

Instrumentation

Particle size distribution studies were conducted using a Malvern Mastersizer 3000 laser diffraction analyzer fitted with Aero S dry dispersion and Hydro MV wet dispersion modules. Collection, processing, and evaluation of particle size data were performed using Mastersizer software version 3.88.

Method Optimization

Particle size distribution analysis was carried out using a Malvern Mastersizer 3000 equipped with a Hydro MV wet dispersion unit. Water was employed as the dispersing medium throughout the study. The refractive index of the sample was set at 1.536, while the refractive index of the dispersant was maintained at 1.330. An absorption value of 0.1 was applied for the sample. Measurements were performed with a sample acquisition time of 5 seconds and a background measurement time of 5 seconds. The obscuration level was controlled within the range of 5–10%, and the stirrer speed was maintained at 2200 rpm to ensure adequate particle dispersion. Each analysis consisted of three measurement cycles. Under the optimized analytical conditions, satisfactory obscuration levels and reproducible particle size distribution results were obtained for d(0.1), d(0.5), and d(0.9), demonstrating the suitability of the method for routine particle size characterization.

Sample Preparation

The sampling unit was completely filled with the dispersant medium, and the accessory settings were configured through the instrument software. The stirrer/pump speed was gradually increased to 3000 rpm to ensure efficient circulation and dispersion of particles. As the dispersant level decreased during operation, additional dispersant was added to maintain the sampling unit at its maximum capacity. Instrument parameters were verified in accordance with the approved standard operating procedure (SOP) for the Malvern Mastersizer 3000 operating in wet dispersion mode using the predefined analytical conditions. Prior to analysis, the system was degassed three to four times to eliminate entrapped air bubbles and ensure stable measurement conditions.

The validated SOP method was then selected from the software, and a background measurement was initiated. The cleanliness and suitability of the system were assessed by monitoring the laser intensity during background acquisition. If the background laser intensity was below 50%, the sampling unit was emptied, cleaned thoroughly, and the procedure was repeated until acceptable background conditions were achieved. Subsequently, the sample was introduced directly into the sampling unit using a transfer pipette while continuously monitoring the obscuration level. Sample addition was continued until the obscuration stabilized within the target range of 5–10%, as indicated by the instrument display. Particle size distribution measurements were then performed, and the resulting data were automatically recorded for further evaluation and interpretation.

Results

Method Precision

Method precision was evaluated by analyzing six independently prepared sample preparations and determining their particle size distribution profiles using the particle size analyzer. The precision of the method was assessed based on the percentage relative standard deviation (%RSD) of the particle size values obtained at d(0.1), d(0.5), and d(0.9). Acceptance criteria specified that the %RSD values for d(0.1) and d(0.9) should not exceed 15%, while the %RSD for d(0.5) should be within 10%. The results of the precision study are presented in Table 1.

Table 1: Method Precision Results

Run No.	d(0.1)	d(0.5)	d(0.9)
1	19.845	39.856	59.845
2	20.126	40.125	60.124
3	20.457	40.215	60.487
4	20.783	40.487	60.754
5	20.951	40.756	61.125
6	21.118	40.982	61.458
Average	20.547	40.404	60.632
%RSD	2.41	1.04	1.00

Robustness

Robustness of the developed particle size distribution method was evaluated by introducing deliberate variations in critical analytical parameters, including obscuration levels (5–10%) and stirrer speed (±200 rpm). The particle size distribution of the sample was determined under these modified conditions, and the corresponding percentage relative standard deviation (%RSD) values for d(0.1), d(0.5), and d(0.9) were calculated. The method was considered robust if the %RSD values for d(0.1) and d(0.9) did not exceed 15%, while the %RSD for d(0.5) remained within 10%. The results obtained from the robustness studies are presented in Tables 2 and 3.

Table 2: Results for Robustness (Agitation Rate)

Run No.	Agitation (RPM)	d(0.1)	d(0.5)	d(0.9)
1	2000	18.950	37.250	56.501
2		20.478	40.111	60.987
3		22.006	42.972	65.474
Average		20.478	40.111	60.987
%RSD		7.46	7.13	7.36
1	2400	19.715	38.685	58.215
2		20.478	40.111	60.987
3		21.241	41.537	63.759
Average		20.478	40.111	60.987
%RSD		3.73	3.56	4.55

Table 3: Results for Robustness (Obscuration)

Run No.	Obscuration	d(0.1)	d(0.5)	d(0.9)
1	5%	19.586	38.245	57.954
2		20.245	40.865	61.458
3		21.603	41.223	63.549
Average		20.478	40.111	60.987
%RSD		5.02	4.05	4.64
1	10%	19.124	38.856	57.765
2		20.632	40.254	61.125
3		21.678	41.223	64.071
Average		20.478	40.111	60.987
%RSD		6.27	2.97	5.17

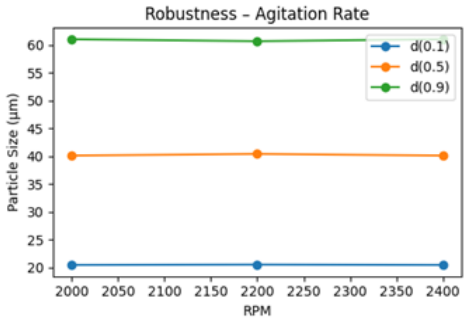

Figure 1: Robustness Variation Agitation Rate

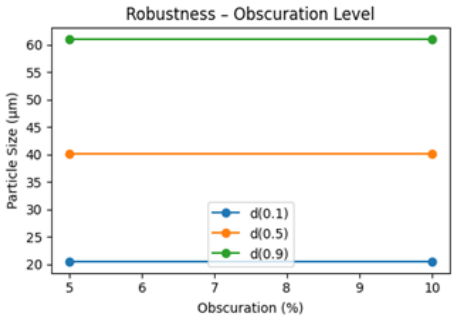

Figure 2: Robustness Variation Obscuration level

Intermediate precision

Intermediate precision was assessed to determine the reproducibility of the developed particle size distribution method. A second analyst independently prepared and analyzed six sample preparations on a different day using the same analytical procedure and instrument settings. Particle size values for d(0.1), d(0.5), and d(0.9) were recorded, and the corresponding percentage relative standard deviation (%RSD) values were calculated. The acceptance criteria specified that the %RSD values for d(0.1) and d(0.9) should not exceed 15%, while the %RSD for d(0.5) should be not more than 10%. The results of the intermediate precision study are presented in Table 4.

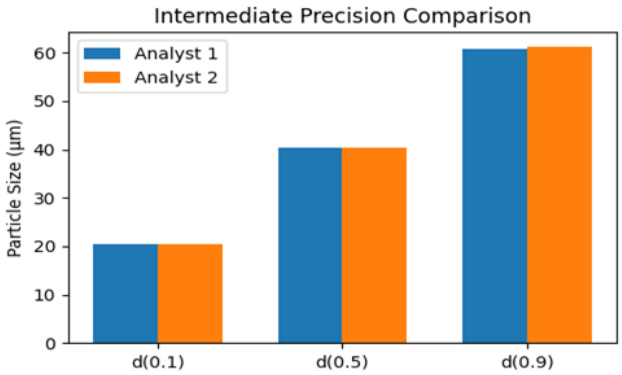

Figure 3: Intermediate Precision Comparison Results

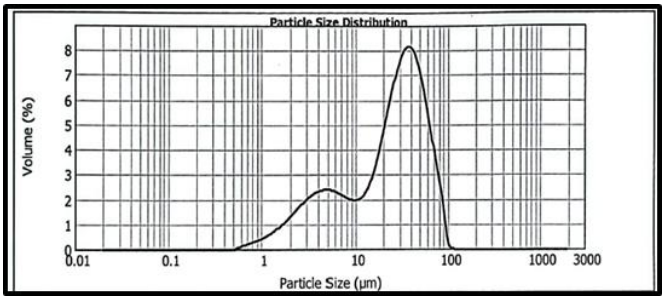

Figure 4: Histogram curve

Table 4: Results for Intermediate Precision

Run No.	User-1			User-2		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
1	19.845	39.856	59.845	18.356	36.985	56.214
2	20.126	40.125	60.124	19.452	38.752	58.693
3	20.457	40.215	60.487	20.128	39.865	60.241
4	20.783	40.487	60.754	20.985	40.754	61.785
5	20.951	40.756	61.125	21.756	42.186	63.924
6	21.118	40.982	61.458	22.465	43.924	65.847
Average	20.547	40.404	60.632	20.524	40.411	61.117
%RSD	2.41	1.04	1.00	7.39	6.10	5.73

Discussion

The present study successfully developed and evaluated a robust laser diffraction method for the determination of particle size distribution (PSD) in Famotidine Oral Suspension USP, 40 mg/5 mL. Particle size distribution is considered a critical quality attribute for oral suspensions because it directly influences sedimentation behavior, redispersibility, content uniformity, dissolution rate, physical stability, and ultimately the therapeutic performance of the product. Therefore, the establishment of a

reliable analytical method for PSD determination is essential for routine quality control and product lifecycle management. The particle size distribution profile obtained from the optimized method demonstrated a multimodal distribution pattern. As illustrated in Figure 1, the distribution curve exhibited a predominant peak centered between approximately 30 and 60 µm, indicating that the majority of suspended famotidine particles were present within this size range. A smaller shoulder peak observed in the lower particle size region suggested the presence of a minor fraction of finer particles. Such a distribution is characteristic of pharmaceutical suspensions formulated to balance physical stability and dissolution performance. The absence of a significant population of oversized particles beyond 100 µm indicated effective particle size control during manufacturing and minimized the risk of rapid sedimentation and dose variability. Method precision studies demonstrated excellent repeatability of the developed analytical procedure. The mean particle size values obtained for d(0.1), d(0.5), and d(0.9) were 20.547 µm, 40.404 µm, and 60.632 µm, respectively. The corresponding %RSD values were 2.41%, 1.04%, and 1.00%, which were substantially lower than the predefined acceptance criteria. These results indicate a high degree of consistency among independently prepared samples and confirm that the method is capable of producing reproducible particle size measurements under identical operating conditions. The low variability observed further suggests that sample preparation, dispersion efficiency, and measurement conditions were adequately controlled throughout the analysis. Intermediate precision studies were conducted to assess the reproducibility of the method under normal laboratory variations, including different analysts and different days of analysis. The second analyst obtained %RSD values of 7.39%, 6.10%, and 5.73% for d(0.1), d(0.5), and d(0.9), respectively. Although slightly higher than those observed during method precision studies, these values remained well within the established acceptance limits. The results demonstrate that the developed method is not significantly affected by analyst-to-analyst variability and provides reliable measurements across different operating conditions. This reproducibility is particularly important for routine quality control laboratories where multiple analysts may perform the analysis. Robustness testing further confirmed the reliability of the analytical procedure. Deliberate variations in agitation rate and obscuration level were introduced to evaluate the sensitivity of the method to minor operational changes. For agitation rate studies, %RSD values remained below 8% for all particle size parameters, demonstrating that moderate changes in stirrer speed did not significantly influence particle size measurements. Similarly, variations in obscuration levels between 5% and 10% produced acceptable %RSD values for d(0.1), d(0.5), and d(0.9). These findings indicate that the method is sufficiently robust and capable of maintaining analytical performance despite small fluctuations in instrument settings and sample loading conditions. Such robustness is essential for ensuring reliable results during routine laboratory operations. The use of water as the dispersing medium and the optimization of critical parameters, including refractive index, obscuration range, and stirrer speed, contributed significantly to achieving consistent particle dispersion and stable measurements. Proper dispersion is particularly important in suspension formulations because particle agglomeration can lead to inaccurate size measurements and increased analytical variability. The optimized conditions ensured efficient particle separation while preventing excessive shear-induced particle breakage. The laser diffraction technique employed in this study offers several advantages over traditional microscopic methods, including rapid analysis, a wide measurement range, minimal operator dependency, and the ability to evaluate a large number of particles simultaneously. These characteristics make laser diffraction particularly suitable for pharmaceutical suspension analysis and routine quality control applications.

Conclusion

The results obtained in the present investigation are also consistent with previously reported particle size characterization studies involving oral suspension dosage forms, confirming the suitability of laser diffraction technology for PSD assessment. Overall, the developed method demonstrated excellent precision, intermediate precision, and robustness, while providing a detailed characterization of the particle size distribution profile of Famotidine Oral Suspension USP, 40 mg/5 mL. The predominance of particles within the desired size range and the low variability observed throughout validation studies confirm the suitability of the method for routine quality control testing, formulation development, manufacturing process monitoring, and stability evaluation. The method can therefore serve as a reliable analytical tool for ensuring consistent product quality and performance throughout the commercial lifecycle of Famotidine Oral Suspension USP, 40 mg/5 mL.

Conflict of Interests

The authors declare no conflict of interest

Ethics Approval

Not applicable

Funding

This study received no specific funding from public, commercial, or not for profit funding agencies.

AI Tool Declaration

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

Data Availability

Data will be available on request

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